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(54) Title: AN IMPROVED METHOD OF FABRICATING CODED PARTICLES

(57) Abstract

This invention relates to an improved method of fabricating silicon microparticles (5, 10, 12, 18, 20, 23, 26), each microparticle (5, 10, 12, 18, 20, 23, 26) carrying a machine readable binary code in the form of holes (2, 3, 6, 13, 15, 17, 24, 27), pits, or other optically identifiable marks. The microparticles (5, 10, 12, 18, 20, 23, 26) may be manufactured in sizes from a few tens of micrometres up to millimetres in linear dimension and simultaneously manufactured in numbers of up to the order of one million from a single silicon wafer (1, 4, 16), depending upon particle size. The process of manufacture is based upon direct etching of silicon wafers (1, 4, 16). Microparticles (5, 10, 12, 18, 20, 23, 26) of a few tens of micrometres length and breadth, which are essentially invisible to the naked eye, may be manufactured by this process for use in security and anti-counterfeiting applications of valuable goods, paper currency, etc. Larger particles (5, 10, 12, 18, 20, 23, 26) of up to several hundred micrometres in length and breadth which additionally carry a quantity of appropriate combinatorial chemistry support polymer resin (11, 14, 19, 21, 25, 29) in the form of a layer or a bead may be made for use in combinatorial compound.library (CCL) synthesis.

An Improved Method of Fabricating Coded Particles

Field of the Invention

The present invention relates to an improved method of fabricating coded particles.

5   It is particularly applicable, but in no way restricted, to the fabrication of coded security particles and coded combinatorial chemistry support particles.

Background to the Invention

A method has been described in GB 2 289 150 B by which small microparticles may

10   be manufactured by the process of silicon micromachining, each microparticle carrying an identifying code in the form of holes, pits, or similar marks constituting a machine readable binary number. The microparticles may be fabricated from typically silicon or silicon dioxide, and have dimensions in the approximate range $0.1\mu m$ to $5\mu m$ thickness and $0.5\mu m$ to $50\mu m$ width and length, rendering them essentially

15   invisible to the naked eye. Suspensions of the coded microparticles (either gaseous, such as in smoke, or liquid such as in paint, clear varnish or ink) would find application in security systems as they may be used to uniquely label items such as consumer durables (cars, motorcycles, electrical appliances) or other valuables (jewellery). Such labelling could be undertaken either during manufacture or at any time

20   subsequently. Similarly, the microparticles could be employed in security printing (particles impregnated in paper or in suspension in printing inks) for items including banknotes or negotiable securities or in other documentation (driving licences, passports, identity cards) where security and uniqueness is a consideration. Identification of the particle codes could be achieved using a hand-held or desktop

25   optical reader similar to bar code readers used in supermarkets. The technology used

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in the readers could be based on that found in compact disc laser readers or by using a conventional imaging device, such as a charge-coupled device array incorporated within suitable microscope imaging optics, the output of the imaging device being processed electronically to determine the identity of the code.

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A variant of these coded microparticles for use in combinatorial chemistry library synthesis is described in GB 2306484 B. This patent describes microparticles of larger dimensions than those discussed above, being typically of greater than 100μm length and width and up to 10μm thickness. Additionally, the microparticles may be

10   encapsulated by, coated with, or otherwise attached to, a polymeric material which acts as a substrate for the chemical compound growth during the combinatorial chemistry process. Unlike the coded microparticles for security applications where a multitude of particles labelling a single item would all carry the same machine readable code, the microparticles for combinatorial chemistry would each carry a

15   unique code, thus allowing individual particles to be tracked throughout the combinatorial compound library synthesis, an essential requirement in allowing the compound synthesis sequence for compounds which exhibit the desired biological, pharmacological or chemical activity to be determined and reproduced. A more detailed description of such a synthesis is given in GB 2306484 B.

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For both the security application and the combinatorial chemistry application, the method of manufacture of the coded microparticles is essentially the same, and is described in GB 2,289150B and GB 2306484 B. For convenience, a brief summary is provided as background information here. The micromachining technology was

25   developed from the microelectronics industry and uses similar processes

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of deposition and etching to those used to make microelectronic integrated circuits. The fundamentals of the fabrication of the microparticles is described by Kaye et. al. in the Journal of Aerosol Science Vol. 23 [1992, Supplement 1, 201-204] and involves typically:- the design of the required particle geometry (or geometries) using

5   computer aided design (CAD) tools; the manufacture of appropriate photolithographic masks which delineate both the microparticle outlines and the required coding marks within the microparticle outlines; the growth by vapour deposition onto a polished silicon wafer (typically 3, 4 or 8 inches in diameter) of a thin layer of material such as aluminium, this to become a sacrificial bonding layer (see below); the growth by

10   vapour deposition or similar process, onto this sacrificial layer of a further layer of, for example, silicon or silicon dioxide from which the particles will be ultimately be formed; the coating of this layer with a photosensitive polymer resist (photo-resist) which, upon ultraviolet exposure through the photolithographic mask, defines the microparticle shapes and the locations of coding marks; the removal of exposed

15   photo-resist thus revealing areas of the underlying layer of silicon or silicon dioxide; and finally the creation of the microparticles with their associated code marks within this layer by etching away the revealed areas of the layer between the microparticle outlines and within the areas designated as code marks. The particles may then be freed from the wafer substrate by dissolution of a sacrificial layer which underlies the

20   particles. The sacrificial layer is typically made of aluminium if the particles are of silicon dioxide, and of silicon dioxide if the particles are of silicon.

In the case of the microparticles for combinatorial chemistry, an additional processing stage is required before the microparticles are freed from the wafer substrate. In this

25   additional stage, each coded microparticle receives its quantity of polymer support

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material attached to the microparticle in the form of a chemically attached surface layer, by mechanical linkage or entrapment, or by some other method of attachment as described in GB 2306484 B. Depending on the size of the microparticles, a wafer substrate may thus be etched by micromachining processes to yield up to a million

5   particles, each, if desired, carrying a different binary code. The microscopic code on the particles may be interrogated and read using contemporary microscope-based image processing systems. By way of example, a code containing just twenty binary sites (pits, holes, or similar devices in the microparticle) would allow a million particles to be uniquely numbered from 1 to 1,000,000.

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The accepted method of manufacture of the coded microparticles as described above is practical but suffers several limitations. Firstly, the method of micromachining by which a layer of silicon or silicon dioxide is grown by vapour deposition or similar process onto the surface of a silicon wafer and subsequently etched to form the

15   microparticles falls within the category of what is called 'surface micromachining'. This is a well established technique in the field of micromachining. However, a layer grown on a surface in this way is normally limited in maximum thickness to of the order of 10-20µm. This is because for thicker layers, the inherent stresses which occur during layer growth can lead to microparticle fracture once the etched microparticles are

20   freed from the host wafer. For many applications in the security field where microparticle widths and lengths may be a few tens of micrometres, microparticle thicknesses of below 10µm are acceptable and therefore the thickness limit is not a problem. However, for larger particles of greater than 100µm length and or width, such as may be required in the combinatorial chemistry applications and notably, for

25   example, where it is desired to achieve a high loading of combinatorial chemistry

support polymer per particle, a thickness of less than 10µm leads to a high surface area to thickness ratio and consequently a mechanically less robust particle. In many areas of use, the particles will have to endure mechanical stress, and particles which exhibit a thin wafer-like form are far more likely to suffer breakage than those of a

5   more isometric geometry.

Secondly, layers grown in the way described above are generally of amorphous form, as in the case of silicon dioxide, or are polycrystalline (being formed from vast numbers of randomly aligned crystallites) as in the case of silicon. In either case, the

10   resultant particles may be comparatively brittle and not as mechanically strong as, for example, single crystal silicon, the material of the supporting wafer upon which the particles are formed.

Thirdly, the release of the etched microparticles from the host silicon wafer (as

15   described in Kaye et al, ibid) requires the dissolution of the thin sacrificial layer between the two. In the case of silicon dioxide particles, this layer may be of aluminium and its solvent concentrated hydrochloric acid. For small surface-area microparticles the removal of this sacrificial layer is not problematic. However, for larger area particles, as would be required in the combinatorial chemistry application,

20   the dissolution of the sacrificial layer can become severely impeded as it progresses into the crevice between the microparticle and the host wafer by the formation and entrapment of bubbles of hydrogen. Unable to escape and very difficult to remove by external agitation, these bubbles effectively insulate the remaining aluminium from attack by the acid, leaving a proportion of the microparticles to all intents and

25   purposes permanently attached to the host wafer and therefore of no practical use.

Fourthly, it is well recognised by practitioners in the field of surface micromachining that freshly exposed surfaces of silicon will strongly adhere if brought into contact. Normally, such freshly exposed surfaces when in air will instantly form a native oxide

5   layer to prevent such adhesion. However, during the manufacture of polycrystalline silicon microparticles as described above, at the moment of removal of the sacrificial layer between particles and the host wafer, silicon surfaces are in very close proximity and are unable to oxidise because of their immersion in the sacrificial layer solvent . In the case of silicon particles this would be concentrated hydrofluoric acid. There is a

10 very strong tendency for freed particles to immediately re-adhere to the silicon surface therefore, again rendering them of no practical use. Measures such as constant ultrasonic agitation have to be used to reduce this re-adhesion, but a proportion of the particles are inevitably lost in this way.

15 Additionally this manufacturing process requires costly and sensitive equipment and is usually carried out in clean room conditions. This inevitably leads to increased manufacturing costs.

In summary, an alternative approach to particle fabrication is required which allows

20 larger particles to be produced without the risk of particle fracture. This need is addressed by the method described in the following section. The section also describes a method by which the codes on these larger particles may be efficiently read, and methods by which further advantage can be gained from the efficient process of code reading and particle tracking which is a feature of the machine-

25 readable coded particles.

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Summary of the Invention

According to a first aspect of the present invention there is provided a method of fabricating coded particles comprising the steps of:-

5   (a)   coating a face of a wafer of silicon or a similar crystalline material or inert metal or metal alloy with a photo-resist polymer;

       (b)   exposing the coated face of the wafer to ultra-violet radiation through an appropriate photolithographic mask, said mask defining the particle size and/or the position of code sites on the particle;

10   (c)   dissolving or otherwise removing either the UV exposed or the UV unexposed areas of photo-resist;

       (d)   etching the exposed areas of the wafer, from which the photoresist has been removed, using an appropriate etching agent; and

       (e)   liberating the particles.

15   This process avoids the disadvantages inherent in conventional micromachining techniques for fabricating coded particles

In a preferred embodiment the wafer is first attached to a stable substrate such as a glass plate, using a thin adhesive layer such as, for example, a layer of wax. The final

20   step in the process is removing the particles from the substrate suitably by dissolving the adhesive or the substrate. This additional feature is particularly applicable to the manufacture of larger particles for use in combinatorial chemistry.

Preferably the step of etching the wafer comprises plasma etching the exposed areas

25   of the wafer through to the opposing face of the wafer.

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In an alternative preferred embodiment the wafer is a single crystal silicon wafer etched by an anisotropic wet chemical etching agent to etch the wafer anisotropically.

5   In a preferred embodiment there is provided an additional step of applying an amount of combinatorial chemistry support polymer to each particle prior to release.

In a particularly preferred embodiment a combinatorial chemistry support polymer is trapped within a recess or cavity that was suitably formed within the coded particle by
10   the etching step.   The polymer might suitably be applied in the form of monomer which is then polymerised or might be applied as shrunk polymer beads that are then allowed to expand to their natural size.

Preferably the code is a machine readable binary code where the term binary code
15   also includes bar codes or, for simple particles, the code may reside in the shape of the particle.

According to a second aspect of the invention there is provided a set of support particles consisting of particles as fabricated above substantially each particle in the
20   set having the same machine readable code.

According to a third aspect of the invention there is provided a set of support particles as fabricated above substantially each particle in the set having a unique machine readable code.

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In a still further aspect of the invention there is provided a combinatorial library prepared using the above support particles, regardless of the chemical reactions or sequences used to prepare said library.

5   The present invention also provides a method of reading codes comprising the steps of:

(a) placing the particles to be read in a substantially flat, substantially horizontal vessel with a transparent bottom, the area of the bottom being at least double the total area of the particles to be measured;

10   (b) agitating the vessel to form a monolayer of particles on the bottom; and

(c) scanning the vessel with an imaging system whilst illuminating the particles.

Brief Description of the Drawings

The present invention will be further described, by way of example only, by reference

15   to the accompanying drawings in which:-

Figures 1 & 2 illustrate perspective and cross-sectional views of typical pyramidal holes etched through a silicon wafer by potassium hydroxide etching agent;

Figure 3 illustrates an array of particles etched with holes as shown in Figures 1 and 2;

20   Figure 4 illustrates a cross-section of a series of particles set in a layer of wax on a glass plate;

Figure 5 illustrates a coded particle with a layer of polymer adhered to part of its surface;

Figure 6 illustrates a cross-section of a particle with polymer set within a hole in the

25   particle;

Figure 7 illustrates a substantially circular bead resting in a hole within a coded particle;

Figure 9 illustrates a particle with a single hole etched through it;

Figure 10 illustrates a cross-section of the particles in Figures 8 and 9 bonded

5   together around a polymer bead;

Figures 11A and 11B illustrate in perspective view plasma etched coded particles onto which one and two polymer deposits respectively have been made; and

Figure 12 illustrates plan and side views of a resin bead trapped within an aperture in a plasma etched coded particle.

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Description of the Preferred Embodiments

In the method described in GB 2306484 B the particles are formed by etching a layer of material which had previously been deposited onto a flat substrate, such as a silicon wafer. In contrast, the improved method described herein involves the

15   etching of the silicon wafer (or other suitable solid) itself to form the particles.

The current invention overcomes the limitations of the prior art as well as providing a method of particle fabrication which is simpler and less dependent upon some of the expensive equipment necessary for thin layer growth on silicon wafers. It also allows

20   the coded particles to be manufactured with any desired dimensions from a few tens of micrometres to millimetres in size.

Ultra-thin single crystal silicon wafers are commercially available. These wafers are slices of silicon from a single silicon crystal which have been polished on both sides to

25   thin them to a wafer thickness of any chosen magnitude from the order of 250µm

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down to 5μm. The wafer diameters may be typically 2 inches or 3 inches. The crystal

orientation of the wafers is usually <100>. One company who manufacture these

wafers is Virginia Semiconductor Inc., of 1501 Powhatan Street, Fredericksberg, VA

22401, U.S.A. One property of single crystal wafers of this type is that certain wet

5   chemical etchants, such as potassium hydroxide (KOH) and ethylene-diamine-

pyrocatechol – water (EDP), will attack the silicon anisotropically, with the effect that

the silicon is removed only to a point where a <111> crystal plane is encountered.

This means that if, for example, a square area of the surface of the silicon is exposed,

the KOH will etch down into the silicon to form a four sided pyramidal pit whose sides

10   represent the four <111> crystal planes. The atomic structure of silicon dictates that

these planes will be at 54° to the <100> plane (the surface of the wafer). If the wafer

is thin in comparison to the diameter of the exposed surface, the etched pit may

extend completely through the opposite surface of the wafer, leading to the formation

of a hole through the wafer. Figure 1 illustrates a section of thinned silicon wafer 1

15   containing such a pyramidal hole 2 . This feature can be put to use in the fabrication

of coded microparticles. The following description is a preferred but not the only

method of processing a thinned wafer to produce such particles.

The preferred thickness of the original silicon wafer is in part determined by the size

20   requirements of the desired coded particles and the nature of the code marks

themselves. It is most beneficial when dealing with opaque materials such as silicon

for the code marks to be in the form of holes through the complete particle thickness

rather than simply surface features, this being because holes allow clear identification

of the code sites by transmission illumination of the particle. If, therefore, a particle is

25   desired to have surface dimensions of 100μm by 100μm, and if it is desired that each

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particle should carry a 16-bit binary code (ie: there should be 16 individual hole-sites, some of which will be etched and others not, so as to define the binary code) arranged in a 4 by 4 array, then the thickness of the wafer must be such that each of the hole sites must be of a size that, when the hole is anisotropically etched using

5   KOH, the bottom surface of the wafer is reached before the etch terminates (ie: reached the apex of its four-sided pyramid). In the example given, for a wafer thickness of 10µm and a desired minimum hole size of 5µm by 5µm at the lower surface (typical dimensions to ensure relatively straightforward microscope imaging of the holes to facilitate code reading), the exposed area of silicon at the upper surface

10 must be 19.52µm by 19.52µm. Figure 2 illustrates a cross-section of such a pyramidal hole 3 in a thinned silicon wafer 4. Thus, a 4 by 4 array of such hole-sites, constituting a 16-bit binary code, would comfortably fit within the perimeter of the 100µm by 100µm microparticle.

15 The preferred process for producing a large number of coded particles for use, say, in a security labelling application would be as follows: The thinned wafer (of, say, 5µm thickness) would be coated on both sides with a photo-resist polymer. The upper surface of the wafer would then be exposed to ultraviolet radiation through an appropriate photolithographic mask which defined the positions of the particles and

20 the positions of the code site holes on the particles. The exposed areas of the photo-resist are then dissolved away using an appropriate solvent, thus exposing the surface of the silicon wafer to the sites where holes are to be etched and to the inter-particle regions which must be removed to produce separated particles. The wafer is then immersed in potassium hydroxide and the exposed areas of the wafer are etched

25 away anisotropically to leave discrete particles suspended on the thin (unexposed)

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photo-resist layer on the lower surface. The code site holes will have been etched too. Figure 3 illustrates the appearance of some of the particles 5 with the code site holes 6 etched in the particles and the inter-particle silicon 7 removed to produce separated particles. Given that the etched area between the particles will be of width

5   approximately 12µm at the upper surface (ensuring a 5µm particle separation at the lower surface), the number of 50µm square particles which could be formed on a 3 inch wafer would be approximately 500,000 with each particle carrying a 16-bit binary code. The final stage is to free the particles from the photo-resist layer by immersion in a further solvent routinely used for removing unexposed photo-resist. The freed

10   particles will sink to the bottom of the vessel containing the solvent, and may be pipetted into a separate container for further washing and ultimate preparation as a dry powder or as a liquid suspension in, for example, a clear lacquer.

The above method offers significant advantages over the current art. Firstly, the

15   particles may be made by this method in almost any size from a few tens of micrometres width and breadth to millimetre-sized width and breadth. Larger particles should be proportionally of greater thickness so as to retain mechanical strength, and this will have a subsequent effect on the spacing between code mark sites because of the pyramidal geometry of etched-through holes.   Thicker wafers will require

20   proportionally greater separation between the code mark sites because the dimensions of the pyramidal holes at the upper surface will be scale with particle thickness. Secondly, the particles are made from single crystal silicon, making them stronger and more mechanically robust than particles produced by the layer growth method. Thirdly, because there is no sacrificial layer to be removed so as to free the

25   particles (as is the case in grown-layer particle fabrication), there are no attendant

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problems with gas bubbles interfering with particle release. Fourthly the absence of a host wafer silicon surface in very close proximity to the newly freed particles means that particle losses by re-adhesion to the silicon will be eliminated. The possibility of particle-to-particle adhesion will still exist, but this is far less of a problem because at

5   the moment of release from the photo-resist layer the particles are separated by several micrometres as opposed to a fraction of a micron as is the case with the sacrificial layer method, and the areas of adjacent silicon are, in relative terms, much smaller. There are fewer process steps involved in the new method of particle fabrication than are involved in the old method, and fewer photolithographic masks

10   are required. The new method of particle fabrication is accordingly significantly less expensive than the old method.

Coded Particles for Combinatorial Chemistry

The new method herein described can also be used to manufacture coded particles for use in combinatorial chemistry library synthesis. In this case, coded particles of

15   larger size than those used in security applications are desirable because the particles must also carry a quantity of polymer resin which supports chemical compound growth, and pharmaceutical technology currently requires this quantity to be of a volume equivalent to that of a sphere of up to several hundred micrometres in diameter, these being the approximate sizes of polystyrene resin 'beads' currently

20   used in combinatorial chemistry drug development processes.

There are several methods by which the polymer resin can be attached to the particle, including: applying a layer of monomer to the silicon particle surface, where it is subsequently polymerised; securing the polymer within a hole within the particle; and

25   creating a physical cage within the silicon particle which is designed to retain a single

spherical polymer bead. These methods are described below. All the methods are based upon the aforementioned particle fabrication process using thinned silicon wafers as described earlier for the security coded particles, with an important additional feature: when the particles, and associated code marks, have been etched

5   as described above and the particles are still attached to the photo-resist layer covering their lower surfaces, the polymer resin must be attached in some way to the particles. The photo-resist layer is too weak to hold the particles firmly whilst this operation is carried out, and a more rigid temporary support for the particles is required. One method of achieving this support is to attach the original naked thinned

10   silicon wafer to a strong flat glass plate using a very thin layer of wax or similar substance. Paraffin wax is useable, but any wax-like material which is impervious to wet chemicals (such as KOH), which is solid and firm at room temperature, which has a melting point above the temperature required for polymerisation of styrene (see below), and which has reasonable adhesion to both the silicon wafer and the glass

15   plate, may suffice. The upper surface only of the wafer is then coated with photo-resist and the particle fabrication process proceeds as before. Once the particles (and code marks) have been etched using KOH, the particles will remain in their relative positions held by the wax layer. Figure 4 illustrates in cross-section this configuration of glass plate 8 with a coating of wax 9 supporting the etched particles 10. As

20   mentioned, the step of attaching the polymer resin to each particle may take various forms, examples of which are described below:

In the simplest method, a thin (typically 25μm) mask of a suitable material such as stainless steel, which has holes etched in it in positions defined such that, when the

25   mask is placed over the particle array held on the wax, the holes align with areas on

the particles where polymer deposition is required. (This is a standard 'silk-screening'
process, commonly used in the electronics industry to pattern electronic circuit
boards). Suitable masks are manufactured by several companies, including for
example, ERA Technology Ltd., Leatherhead, Surrey, U.K. A monomer solution of,

5   for example, styrene (since polystyrene is the most common compound growth
support material), is then applied by a spreading process through the mask so that,
when the mask is removed, each particle is left with an area of its surface coated with
monomer styrene. The temperature of the whole assembly (glass plate plus attached
particles) is then raised in an oven to between typically 60° and 80° Celsius

10   whereupon the styrene polymerises. (This polymerisation is catalysed using an
appropriate chemical activator used routinely by practitioners in the field of polymer
chemistry). Finally the whole assembly may be immersed in water or similar liquid
whose temperature is raised to the point where the wax layer melts and the-particles
are freed from their support. An individual particle would then appear as illustrated in

15   Figure 5, with the polymer 11 occupying part of the upper surface of the silicon
particle 12 and the encoding holes 13 occupying the remainder of the upper surface.
The particles may then be collected as before and either resuspended in an
appropriate liquid or rendered as a dried particle collection ready for use in
combinatorial compound library synthesis.

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An alternative method of applying the polymer is now described. The thinned silicon
wafer is attached as before to a rigid glass plate using an appropriate wax or similar
bonding agent. Then, in addition to etching the code holes in the particles and the
inter-particle gaps, each particle is etched with a single (or possibly a plurality of)

25   additional holes 15. The styrene (or similar) monomer is applied as before through a

mask but this time the monomer fills the new hole(s) in the particle. The remainder of

the processing is as before, and the final particle would take the form illustrated in

Figure 6, with the polymer 14 retained within the large hole or holes 15 in the silicon

wafer 16, leaving the code site holes 17 unobscured and viewable using a suitable

5   microscope imaging system or similar. The advantage of this method of attaching the

polymer to the silicon particle is that the exposed surface area of the polymer is

maximised, thus enhancing the polymer's performance in acting as a substrate for

compound growth in subsequent combinatorial compound library synthesis.

10   By way of example, a further embodiment of the method of attaching a polymer resin

to a coded silicon particle is described now. The thinned silicon wafer is attached as

before to a rigid glass plate using an appropriate wax or similar bonding agent. The

particles and associated code holes are etched, but an additional large hole is etched

at the same time within each silicon particle. This large hole will be of essentially

15   square form and, in accordance with the nature of KOH anisotropically etched holes,

will have side walls at 54° to the horizontal particle surface. The size of the hole is

designed such that a conventional polymer resin bead (as currently used in

combinatorial compound library synthesis) may be selected with a diameter which is

less than the aperture in the upper surface of the silicon particle but greater than the

20   aperture in the lower surface. Whilst the silicon particles are still held in place on the

wax bonding layer, the whole of the area covered by the silicon particles on the glass

plate is immersed in dry polymer beads. Single beads will become lodged in the large

etched holes, like marbles in a bagatelle board, such that when the glass plate

supporting the silicon particles is tilted sufficiently, loose beads will roll off, leaving

each silicon particle with an associated lodged polymer bead. Figure 7 illustrates a single silicon particle 18 with a single lodged polymer bead 19.

5   A second thinned silicon wafer is now prepared in a similar fashion to the first, but in this case the wafer is etched in such a way that each resultant silicon particle is in the form of a square 'frame' as in Figure 8, the frame being made with an upper-aperture size sufficient to pass over the lodged bead in the coded silicon particle. The glass plate supporting the second set of particles is then inverted and placed over the first set in such a way that the polymer beads become trapped in cavities produced by the

10   juxtaposition of the large holes in both lower and upper particles. Figure 9 illustrates one of the resulting coded particles 20 containing a single entrapped polymer resin bead 21, held in place within the cavity formed by the coded particle and the inverted square silicon frame 22. The bonding of the frame 22 to the coded particle 20 may be achieve either using a suitable anaerobic adhesive, or by the process of anodic

15   bonding, an established method in the field of silicon micromachining for joining silicon surfaces. The bonding of two discrete silicon components to form a composite particle may be accomplished in a number of ways. For example, the two components may be of different thicknesses, the coded silicon particle being thin in comparison with the frame element retaining the polymer bead. Other geometries of composite particles

20   containing an entrapped polymer bead may also be envisaged, and may employ more than two component parts per composite particle.

In the initial embodiments of method described above thinned silicon wafers are anisotropically etched using a potassium hydroxide etchant to produce particle

25   boundaries and pyramidal-shaped code holes which follow crystal planes.

However, one disadvantage of this initial approach is that, because the holes are pyramidal, their size (in order to penetrate through the particle) is governed by the wafer thickness from which the particle is formed, with thicker wafers requiring larger and more widely spaced code-holes. For thicker wafers therefore, this can

5   limit the size of the code number which the particle can support.

In a further embodiment of the invention most suited to combinatorial chemistry applications, double-sided polished silicon wafer is suitably first anodic-bonded to a substrate material such as glass or by other means to other rigid material such as

10   an organic solid. In the preferred embodiment a Pyrex glass wafer is used.

However, any suitable substrate may be used which has sufficient mechanical strength and chemical stability to withstand the rest of the process. This includes certain rigid polymers and wax blocks, such materials being selected by the

15   materials specialist.

The upper surface of the silicon wafer is then coated with an appropriate photoresist material which is subsequently exposed to ultraviolet radiation through a photolithographic mask which defines the size and shape of the particles and their

20   respective code marks. The particle size thus defined will be selected in accord with the wafer thickness, such that the length and width dimensions of the particle are preferably several times the particle thickness so as to ensure a high probability that a free particle will lie horizontally, thus facilitating code reading. For a 300 micrometre thick wafer therefore, particles of the order of 700 micrometres square

25   would be appropriate. Thinner wafers would allow commensurately smaller cross-

sectional dimensions. Either the UV Exposed or the UV Unexposed areas of photoresist are removed by an appropriate solvent to expose unwanted areas of the silicon surface. These unwanted areas are the inter-particle material plus the sites in the particle defining the code marks.

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A deep plasma etch process may then be used to etch the exposed material of the silicon wafer through the entire wafer thickness but without any etching of the underlying bonded glass wafer: the etching stops at this interface. Both the particles and their code 'holes' are thus formed in the same operation.

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Plasma etching machines capable of etching through the entire depth of a wafer are relatively new tools for use in micromachining. One suitable such system is marketed by Surface Technology Systems Limited of Newport, Gwent, Wales. It is capable of etching through silicon to depths of hundreds of microns and involves

15   intermittent deposition of fluorocarbons to protect the walls of the channels being etched by the plasma. Such systems offer the unique benefit of allowing vertically-sided channels to be etched through the entire silicon thickness. This is in contrast to other etching processes which either 'undercut' the masked areas of silicon or are constrained to follow crystal planes (such as is the case with a potassium

20   hydroxide wet etch). Such Plasma etching therefore allows the high precision fabrication of coded particles with the minimum inter-particle and inter-hole area wastage. The resulting etched glass-silicon composite wafers are then subjected to normal microengineering operations to remove photoresist masking layers and any contamination. Subsequent to this a silicon dioxide layer is deposited (typically

25   30nm) onto the surface of the etched particles in order to provide an optimal surface

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for the subsequent adhesion of polymer resin, as described below.

The support compound for combinatorial chemistry synthesis is then affixed to to each particle, mechanically or chemically, to provide the compound growth platform.

5   In a preferred embodiment, the afore-described method of 'silk-screening' the polymer onto each particle is used.

The polymer mix, prior to curing and consequent cross-linking, is applied though the "silk-screening" mask using a screeding, painting, or rolling process. The silicon

10   dioxide surface may also be advantageously pre-treated with a silane compound designed to provide a 'coupling' functionality between the silicon dioxide and the polymer, hence promoting good adhesion. Also, the area of the particle surface to which polymer is to be applied may itself be etched by appropriate masking and plasma etching to leave a well or wells into which the polymer is forced, again

15   promoting good adhesion between the particle and the polymer.

The use of a silk-screen mask in this way allows accurate simultaneous deposition of polymer to each particle on the wafer, possibly many thousands of particles in total. As indicated in Figure 11, each particle 23 would thus exhibit a code in the

20   form of holes 24, and an area or several separate areas of polymer 25. The exact positions of code holes and polymer would be such as to ensure unobscured viewing of the code holes 24. Once the polymer 25 has been deposited in this way, the temperature of the whole wafer assembly may be raised to an appropriate level to ensure cross-linking of the polymer takes place, whereupon the bond between

25   the polymer and the particle becomes permanent. Finally the resulting polymer-

patterned glass silicon composite wafer may be immersed in hydrofluoric acid in order to dissolve ('sacrifice') the glass substrate, thereby releasing the discrete silicon particles into the acid. The acid may be subsequently removed and the particles recovered for use.

5

In some cases the use of an encapsulating layer (for instance a wax-like compound) resistant to HF to protect the upper surface of the silicon-glass composite subsequent to polymer application and curing would be advantageous. This facility would serve both to protect the aforementioned silane and additionally provide for

10   the use of a polymer other than polystyrene which may be desirable for chemical compound synthesis reasons as such alternative polymers may not share the attribute of polystyrene of being unaffected by immersion in hydrofluoric acid, HF. The glass would then be dissolved by HF from below with the encapsulation protecting the upper surface layer from attack. Subsequent to HF processing the

15   encapsulating layer would be dissolved or melted in a manner compatible with the polymer.

In an alternative method of linking the polymer to the coded particle, conventional polymer resin beads, currently widely used in combinatorial chemistry as solid

20   phase supports for compound growth, may be used. This has the advantage that the chemistry of the beads is well characterised and would therefore be amenable to current synthesis practice. In a further preferred embodiment, resin beads are sieved through appropriate precision sieves so as to separate out a population having a narrow size distribution. For example, beads may be sieved to produce a

25   monodisperse population of nominally 400 +/- 5 micrometres in size. The etching of

the silicon wafer to produce the coded particles proceeds as before, but with the addition that a locating hole is etched in each particle into which a polymer resin bead will subsequently be positioned. As illustrated in figure 12, the particle 26 would exhibit code holes 27 plus a bead entrapment hole 28 which is of a size and

5   form designed to rigidly hold the bead 29 in position whilst allowing the bead 29 to act as a suitable substrate for compound synthesis.

A preferred method by which the beads are positioned in the entrapment holes is as follows. The beads are known to swell and contract when in contact with the various

10   organic solvents used in combinatorial chemistry. It is essential that the bead and host coded silicon particle remain in contact throughout the combinatorial process. The size of the entrapment hole is therefore chosen to be fractionally less than the smallest size which the bead is likely to assume during processing. This would normally occur when the bead is immersed in diethyl ether or similar reagent. The

15   polymer beads may be linked to the silicon particles in the following way. When the silicon particles are etched but still attached to the glass substrate, the suitable population of resin beads is prepared by immersion in diethyl ether, causing them to contract to minimum dimensions. The collection of beads is then poured over the wafer surface and a roller or similar device used to compress the beads against the

20   silicon particles. In areas where a bead becomes positioned over an entrapment hole, the bead will be forced into the hole. Repeated cycles of this process will ensure that the vast majority of the particles entrap a bead. Loose particles may then be flushed away and the wafer immersed in hydrofluoric acid as before to release the particles from the glass substrate. Each silicon particle will then contain

25   a polymer resin bead exposed on upper and lower surfaces, allowing expansion of

23

the bead without it being dislodged from the host silicon particle.

It is intended that this disclosure should encompass particles made from material other than silicon. Any suitable material can be used providing it will undergo the process steps described or their technical equivalent. For example, metals such as gold or compounds such as silicon dioxide could be substituted for silicon.

Reading the Codes

In the original patent (GB 2306484 B), the coded particles therein described were small enough to be manipulated by suspending the particles in liquid and initiating suitable liquid flows. In this way, for example, a flow of particles could be made to pass through the sensing region of a code reading station (based on a digital imaging system) to allow the acquisition of images of the particles and subsequent reading of the codes. In the present invention where larger particles are used (in order to support a larger volume of polymer resin for compound growth), the use of liquid flows to move particles through a reading station is more difficult because of the negative buoyancy of the particles. An alternative method is therefore preferable.

In a presently preferred method, the collection of particles whose codes are to be read are poured onto the transparent surface of a flat horizontal vessel or similar container. Many thousands or many tens of thousands of particles may be involved. The particles may be dry or wetted with one of the liquid reagents used in combinatorial chemistry. The flat surface of the vessel is chosen to have an area several times that of the total surface area presented by the particles when lying

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flat, so that particle overlapping is minimised. The vessel is then placed onto a

suitable mechanically driven stage which allows movement of the vessel in either an

'x – y' motion 'or x + rotation' motion. The vessel is then viewed from above by the

stationary imaging system which is capable of acquiring still images of the particles.

5   By moving the stage in an 'x – y' raster scan beneath the imaging system, it can be

ensured that all the particles contained within the vessel are at some time brought

within the field of view of the imaging system, and their code information recorded.

Alternatively, an 'x + rotation' motion stage will allow the surface of the vessel to be

scanned in either a spiral scan or a series of concentric circular scans. Again, at

10   some time all particles will be brought within the field of view of the imaging system.

Illumination of the particles can be from below, in which case the code holes appear

as bright spots against a dark background, or from above, in which case (because

of the surface reflectivity of the silicon) the code holes appear as dark spots against

a light background. Both forms of illumination can be used sequentially to ensure

15   optimal imaging of the particles and hence greatest accuracy in reading the codes.

The process of reading the code information from the recorded images of particles

is as described in GB 2306484 B. It would also be possible to configure the

mechanically driven stage such that the vessel is vibrated rapidly. This may be

useful to ensure at the start of the scanning process that any particles which rested

20   on their side would topple to the more stable flat orientation required for code

reading. In the normal course of events, however, the particles are considered to be

static within the vessel such that the images of the particles can be used to not only

determine the codes on individual particles but also, in conjunction with a

knowledge of the stage motion, the position of each particle can be evaluated.

25   Knowledge of the position of each particle at and after the final code reading

process can be of value because it allows the user to either manually of robotically

find and extract a particle or particles of choice. Examples of the use of this facility

are given below.

5   In the examples given the etched holes forming the code are substantially square.

However, any shape of hole is possible and the sides of the holes need not

necessarily be linear.   Grooves are also possible and these grooves could form a

surface pattern in the form of a bar code. In relation to the present invention the term

"binary code" includes bar codes in all their various forms.

10

Whilst the codes have been described as pits or holes etc there are many other forms

that these codes can take. In an alternative form the code resides in the shape of the

particle where the shape is chosen from a series of shapes.

15   One method has been described for trapping a support bead within a cavity. But this

is not the only way that this can be achieved.   This invention is intended to

encompass all methods by which a combinatorial support particle bead is trapped in,

on or by a coded particle of this type, however so formed.

20   The present invention also encompasses a library of combinatorial chemistry support

particles and combinatorial libraries formed thereon, regardless of the chemical

reactions or sequences used to prepare said library.

The photo-resists, reagents and polymer supports are given by way of example only.

25   Preferred materials upon which to conduct the synthesis of Combinatorial Chemical

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Libraries (CCL's) are porous silicates, for example controlled pore glass, polymeric resin materials for example polystyrene; poly(substituted-styrene), for example poly(halomethylstyrene), poly(halostyrene), poly(acetoxystyrene); polyacrylamides, for example poly(acryloylsarcosine methyl ester); other polyesters, polyacrylates and

5   polymethacrylates; as well as derivatised versions of these resins, for example polystyrene which has been chloromethylated, or poly(acryloylsarcosine methyl ester) wherein the ester has been saponified and the resultant acid derivatised with another moiety of utility in CCL synthesis, as well as optionally cross-linked versions of these resins.

CLAIMS

1.   A method of fabricating coded particles comprising the steps of:

(a) coating a face of a wafer of silicon or a similar crystalline material or inert metal or metal alloy with a photo-resist polymer

5   (b) exposing the coated face of the wafer to ultra-violet radiation through a photolithographic mask, said mask defining the particle size and/or the position of code sites on the particles;

(c) dissolving or otherwise removing either the UV-Exposed or the UV-Unexposed areas of photo-resist polymer;

10   (d) etching the exposed areas of the wafer, from which the photoresist polymer has been removed, using an appropriate etching agent;

and

(e) liberating the particles.

2.   A method as claimed in claim 1, wherein the wafer is attached to a stable
15   substrate such as a glass plate using a thin adhesive layer and wherein the step of liberating the particles involves dissolving the adhesive layer and/or the stable substrate.

3.   A method as claimed in claim 1 or claim 2, wherein the method comprises an
20   additional step of applying an amount of combinatorial chemistry support polymer to each particle prior to the step of liberating the particles.

4.   A method as claimed in claim 3, wherein in said additional step the combinatorial chemistry support polymer is applied initially in the form of monomer
25   and then treated for polymerisation to occur.

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5. A method as claimed in claim 3 or claim 4, wherein in the step of etching the exposed areas of the wafer one or more areas are etched to provide a recess or cavity into which the combinatorial chemistry support polymer is subsequently

5 entrapped.

6. A method as claimed in claim 1 or claim 2 wherein the step of etching the exposed surface of the wafer is carried out using plasma etching whereby the wafer is etched right through to the opposing face of the wafer.

10

7. A method as claimed in claim 1 or 2 wherein the wafer is a single crystal wafer and the step of etching the exposed surface of the wafer is carried out using potassium hydroxide or another suitable anisotropic wet chemical etchant to etch the wafer anisotropically.

15

8. A method as claimed in claim 3, 4 or 5, wherein prior to the step of applying the combinatorial chemistry support polymer there is a further step of depositing silicon dioxide onto the exposed surface of the particles to assist binding of the combinatorial chemistry support polymer.

20

9. A method as claimed in claim 8, wherein the silicon dioxide is treated with a silane compound to further improve binding of the combinatorial chemistry polymer.

10. A method as claimed in any preceding claim, wherein the code is a machine

25 readable binary code.

11.   A method as claimed in any preceding claim, wherein the code resides in the shape of each particle.

5   12.   A method as claimed in claim 5, wherein the combinatorial chemistry support polymer is in the form of one or more beads that are shrunk prior to insertion into the recess or cavity in each particle and are subsequently allowed to expand to their natural size.

10   13.   A set of coded particles fabricated by the method of any preceding claim, substantially each particle in the set having the same machine readable code.

14.   A set of coded particles fabricated by the method of any of claims 1 to 12, substantially each particle in the set having a unique machine readable code.

15

15.   A combinatorial chemistry library prepared using the coded particles of claim 14, regardless of the chemical reactions or sequences used to prepare the library.

16.   A method of reading codes on coded particles fabricated according to any

20   preceding method claim, the method of reading the codes comprising the steps of:

(a) placing the particles to be read in a substantially flat, substantially horizontal vessel with a transparent bottom, the area of the bottom being at least double the total area of the particles to be measured;

(b) agitating the vessel to form a monolayer of particles on the bottom; and

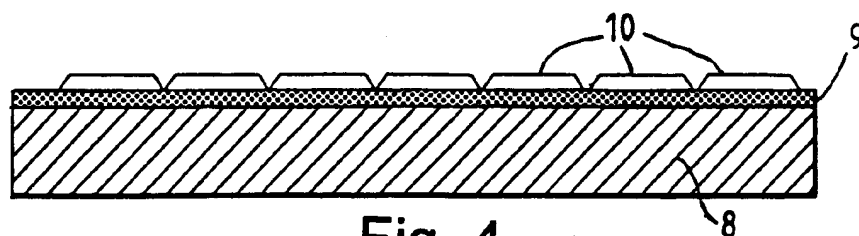25   (c) scanning the vessel with an imaging system whilst illuminating the particles.
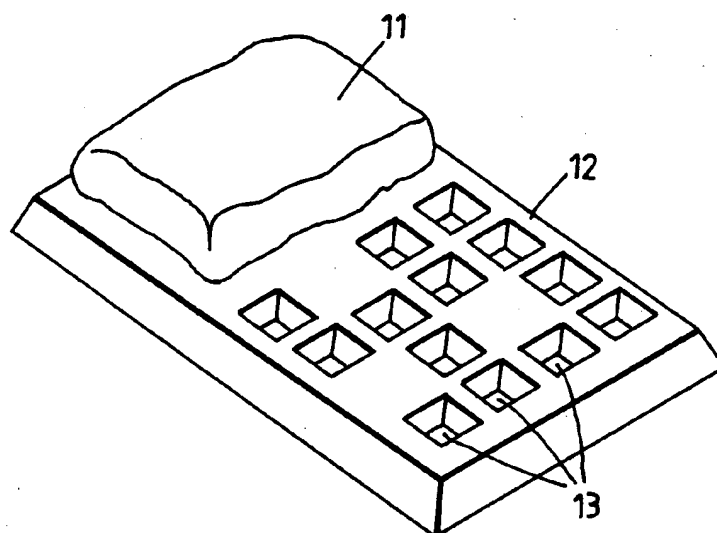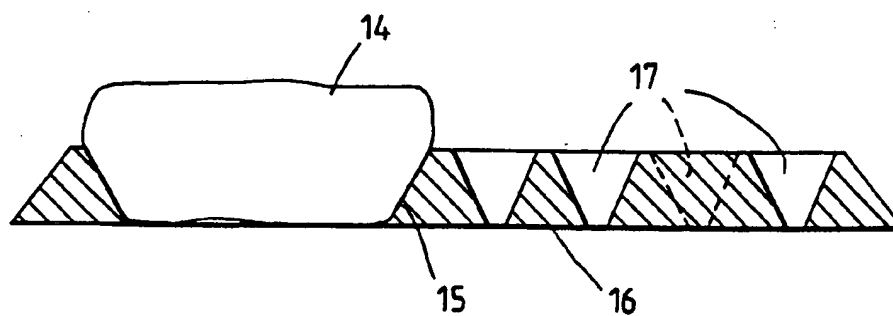
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Fig. 1

Fig. 2

19·52 µm

54° 54°

5µm

Fig. 3

Fig. 4

Fig. 5

Fig. 6

Fig. 7

19

18

Fig. 8

Fig. 9

21   22   20
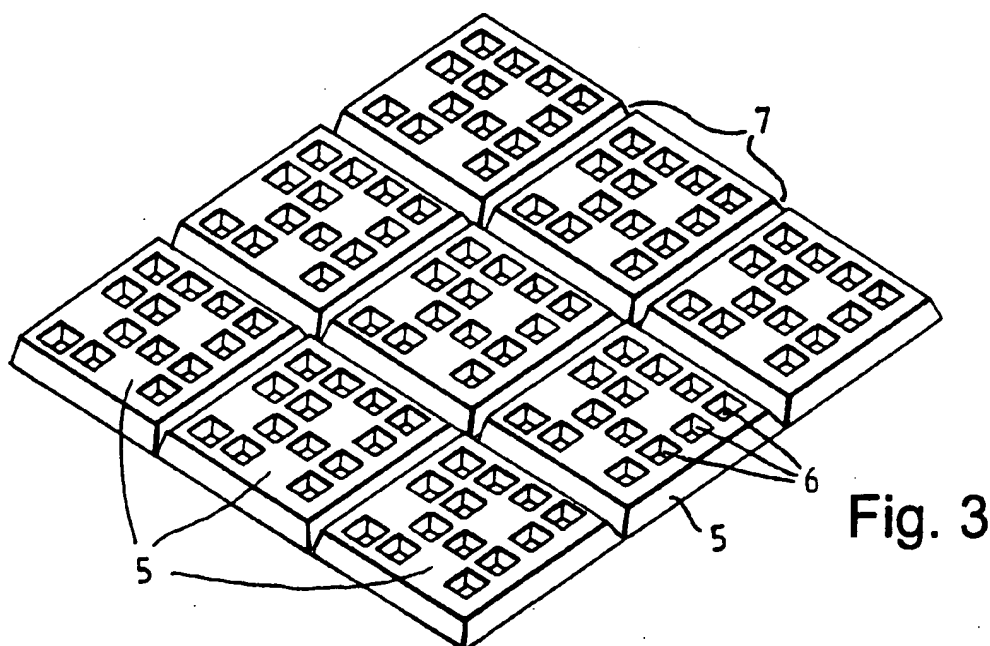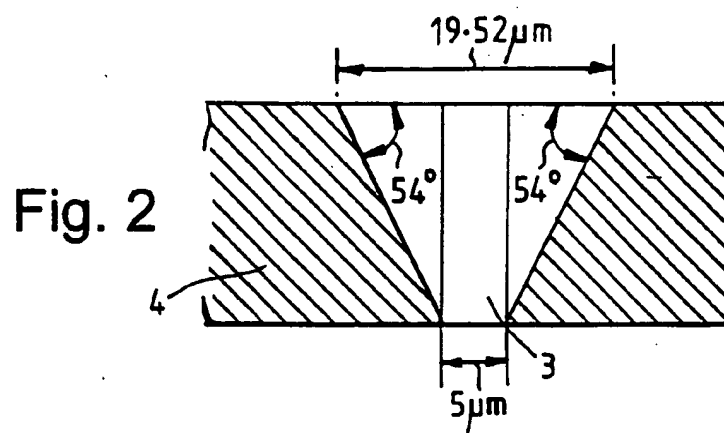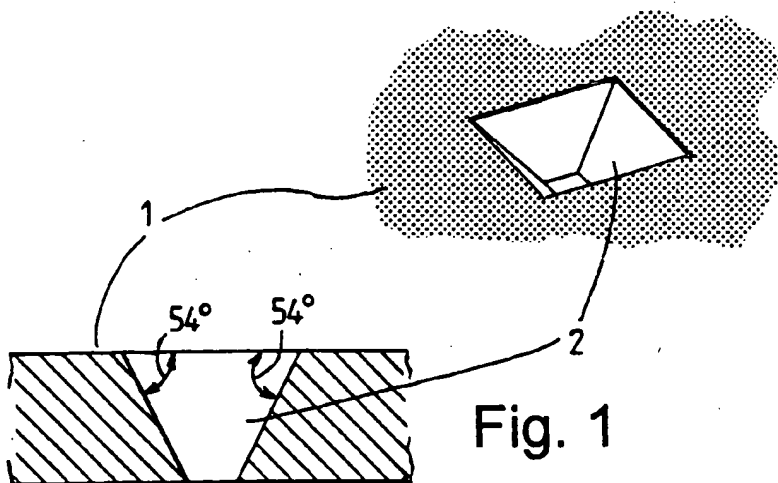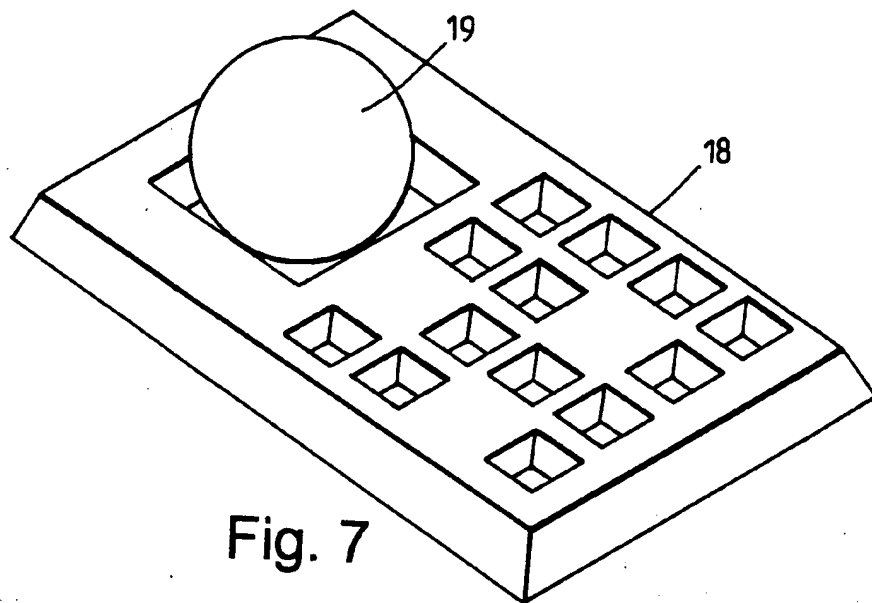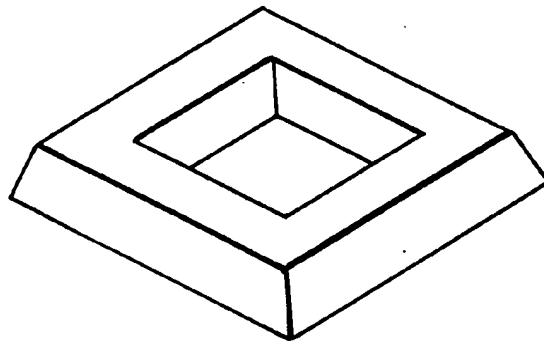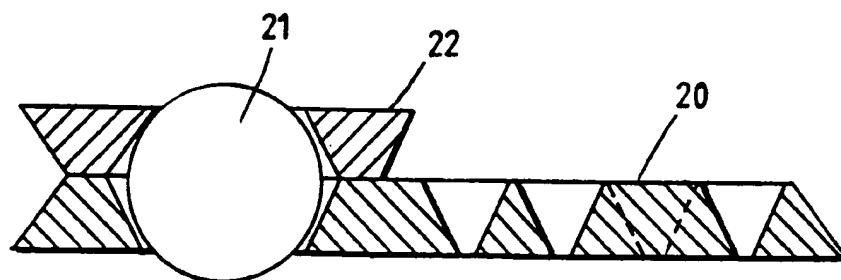
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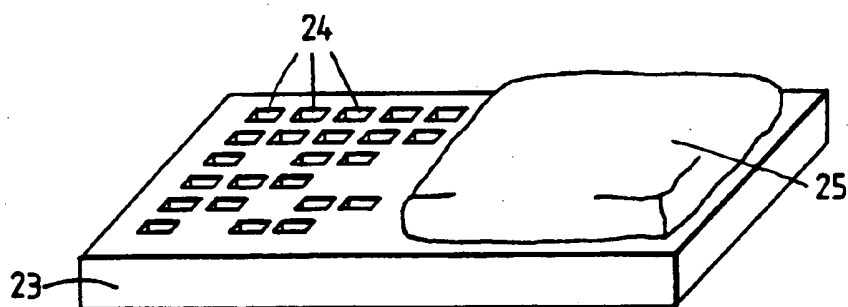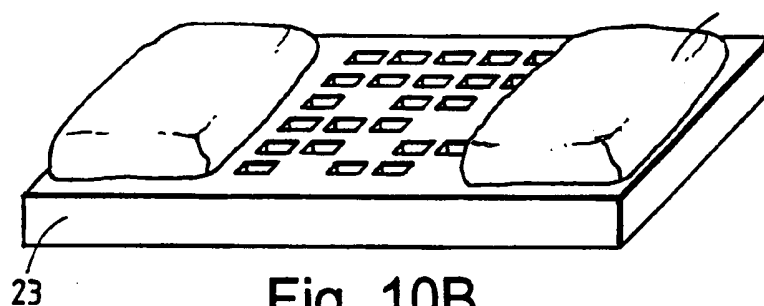
Fig. 10A

Fig. 10B
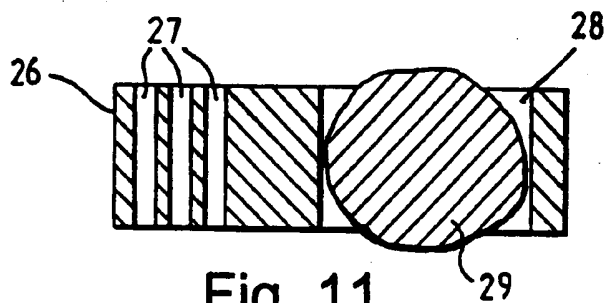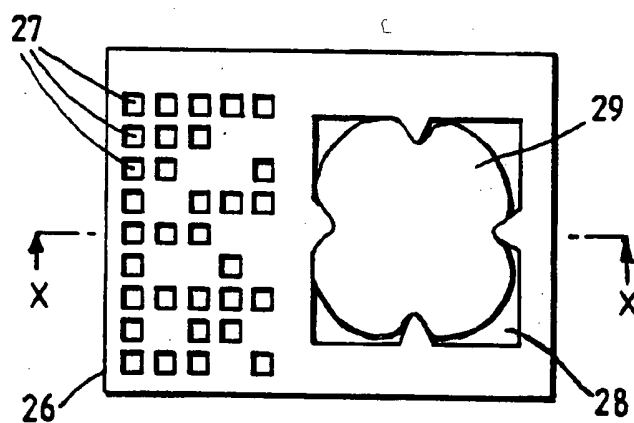
Fig. 11

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6   B01J19/00   B01J13/02   G03F7/00   G09F3/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6   B01J   G06K   G09F   G03F   B81C   B81B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 2 306 484 A (UNIVERSITY OF HERTFORDHIRE) 7 May 1997 cited in the application see page 6, line 24 - page 8, line 11 see page 9, line 21 - line 26 see page 10, line 16 - page 18, line 12 see page 19, line 24 - page 21, line 14 see figures	1,3,5, 10-16
A	---	4,8,9
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| X | Further documents are listed in the continuation of box C. | | X | Patent family members are listed in annex. |

° Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 May 1999	04/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stevnsborg, N

Inte ional Application No
PCT/GB 99/00457

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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